UPON THE SERO-DIAGNOSIS OF GONORRHEA.*

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The most epoch making event in the history of syphilis, is, undoubtedly, the application of the reaction for its diagnosis by Wassermann, which, at present, is justly considered a success. About ten years ago Müller and Oppenheim [1] began to utilize the same reaction, in a similar manner, for the diagnosis of gonorrhea. To American investigators, Teague and Torrey [2] and especially to Schwartz and McNeill [3], who were the first to use a polyvalent gonorrheal antigen, belongs the credit of having rendered the test available for clinical purposes. A careful perusal of the literature, concerning the practical value of the test, reveals the following facts:

The test is always negative in the incipient and early stages of acute gonorrhea, since antibodies do not appear in the blood until at least 21 days have passed after the onset of an acute gonorrheal urethritis. A positive reaction during the course of an acute gonorrhea is, therefore, significant of a previous infection.

A triple and double plus reaction points to the presence of a gonorrheal focus in the body.

In certain severe types of gonorrheal infection the positive reaction may persist for some time after cure has been effected.

A slight or single plus reaction is of doubtful diagnostic significance.

By a negative reaction gonorrheal infection cannot be excluded, and only in the absence of gonorrheal symptoms a negative reaction is of diagnostic significance.

The complement fixation test, if done lege artis, and by means of a polyvalent antigen, may be considered an accurate method of detecting latent gonorrhea.

In contradistinction to the difficulty and unreliability of the bacteriological and cultural diagnosis of chronic gonorrheal infection, particularly in connection with the question of its permanent extinction, the complement fixation test seems to offer a practically important and, also, on account of the many laboratory facilities, available at present at medical centers, a readily accessible source of information. Statements, though, upon the diagnostic accuracy of the test are at variance. A high percentage of positive findings in non-gonorrheal cases and the contradictory reports of the same serologist with the same blood, as recently observed by Uhle and Mackinney [4], tend to detract from the test the practical signifance ascribed to it by other observers.

I, therefore, decided to verify or refute contradictory views upon mooted points by trying the test out on my own material.

The blood for the test was obtained in the same manner as for the Wassermann from one of the arm veins near the elbow, and was, with the exception of a few cases, secured by the serologist, Dr. E. E. Johnson. The test was made by means of several polyvalent antigens (McNeil's, Hirschfelder's and an antigen prepared at the laboratory of Drs. Gilman and Johnson). It will not be amiss to give a brief description of the various antigens used in the tests of our material.

In Hirschfelder's antigen suspensions of various strains of gonococci are mixed with alkaline pancreatine, heated to 38° C and allowed to stand at this temperature for 15 minutes; the mixture is then neutralized with HCL and filtered through a Pasteur filter.

Schwartz and McNeil [5] allow suspensions of gonococci to remain in saline solution for several hours, without shaking, at a temperature of about 37°C. They are then kept at a temperature of 56° C for 30 minutes; placed in a shaker for 24 hours and centrifugalized; the supernatent fluid is pipetted off and used as antigen.

Gilman and Johnson prepare their antigen from 25 different strains of gonococci, which are suspended and cultured on Hirschfelder's testicular extract medium for periods varying between 18 and 48 hours. They claim their medium to assume a higher antigenic value by cultivating their strains at variously long periods of time. The suspensions are then heated at 56° C for three hours, centrifugalized, and filtered through a Berckfeldt filter. The filtrate represents the finished antigen and owes its antigenic value to the endotoxins contained therein.

Tests were made systematically at repeated intervals on patients of the urological service of the German Hospital, which, as a rule, contains a variety of clinical lesions of the genito-urinary tract, including gonorrheal cases, amounting to 150% as an average. In the same manner a number of ambulatory cases were examined at my office. Altogether 142 tests were made on 127 individuals.

Positive reactions were, according to the intensity of complement fixation, designated as one, two and three plus. As with the Wassermann it was deemed best to exclude the one plus reaction from diagnostic deductions, as too indefinite, and to consider it, under exceptional conditions only, as positive evidence.

In 24 cases a three plus, in 17 a two plus, in 25 a one plus and in 76 cases a negative reaction was obtained.

Of the 25 cases with a three plus reaction, all or 100%, were gonorrhoics; 23 or 92.4% suffered from clinical chronic lesions; of the remaining two, one had acute gonorrhea of three weeks standing, while the other, with negative findings, gave a history of previous gonorrheal infection.

Of the 15 cases with a two plus reaction, all

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1 Weiner Klin. Woch., 1906, No. 19, pg. 894.

2 Journ. of Med. Res., 1907, No. 17, pg. 223.

3 Am. Journ. of Med. Sc., May, 1911, pg. 673.

4 N. Y. Med. Journ., Oct. 15, 1915.

5 Am. Journ. of Med. Sc., Dec., 1912, pg. 815.

or 100%, had clinical symptoms of chronic gonorrhea..

Of the 24 cases with a one plus reaction 21, or 83%, had old gonorrheal lesions, while three cases of sexual neurasthenia denied previous infection and gave negative findings. In seven cases of this group gonorrheal complications (two joint-affections, two prostatic abscesses, two strictures of the anterior urethra, one recurrent bilateral epididymitis) were present. Of the 75 cases, with a negative reaction, 42 were symptomatically or anamnestically intact, and six had acute gonorrhea of less than four weeks duration (not applicable to complement fixation). These 48 clinically negative cases, or 65%, thus corresponded with the negative result of the test, while 27 cases, or 35%, presented chronic gonorrheal lesions. Of these five cases, or 6%, demonstrated severe gonorrheal conditions (stricture, arthritis, chronic vesiculitis, etc.).

In 47 cases the Wassermann of blood was made simultaneously. In 23 cases both reactions were negative. In six cases, exhibiting a triple or double plus Wassermann reaction, the complement fixation test was negative, while in seven cases, in which that test was two or three plus, the Wassermann was negative. A positive reaction to syphilis and gonorrhea, simultaneously, was ascertained in two cases, and then it was one plus only in either conditions, an observation which tallies with that of Gardner and Clowes[6], who in a series of 185 cases found in only seven, or 10%, a positive reaction for both gonorrhea and syphilis. It is furthermore stated by experienced serologists, that the presence of active syphilitic antibodies in the blood seems to interfere with complete and ready haemolysis in the gonorrheal test.

A comparison of the clinical with the serological findings in our material, demonstrated quite interesting and, occasionally, perplexing results:

Of 92 cases with a gonorrheal history or gonorrheal clinical symptoms the reaction was
in 20 cases or 22% one plus
in 39 cases or 42% two or three plus
in 32 cases or 35% negative.

The great majority of the latter class were either cases of acute gonorrhea or of chronic prostatitis without positive findings of gonococci; but there were also in this class a number of severe active gonorrheal complications (arthritis, stricture of the anterior urethra, vesiculitis, etc.).

Among 48 cases, with neither clinical symptoms nor a history of gonorrhea, the complement fixation test was negative in 44 cases, or 92%, and positive in four cases, or 8%.

For the most common type of chronic gonorrhea viz: prostatitis the test gave the following results:

It was neg. in eight cases or in 16%,
1 plus in 13 cases or 27%,
2 plus in 15 cases or 30%,
3 plus in 13 cases or 27%.

Counting the one plus with the negative, and the two and three plus with the positive reactions, the figures for this class of cases are 57% positive and 43% negative reactions.

Eight cases of uni- or bilateral epididymitis gave in three cases, or 37.5%, a negative and in five cases, or 62.5%, a positive reaction.

Three cases of gonorrheal arthritis gave in 100% a negative reaction.

Five women with suspicious vaginal discharge, but negative findings of gonococci, gave in 100% a negative reaction.

Of seven cases of urethral stricture the reaction was negative in three cases (40%) one plus in two cases (30%) and three plus in two cases (30%).

In 17 cases the test was repeated within a month. In nine instances the negative reaction remained the same at the second examination. In two cases a two and three plus reaction was obtained both times, in one case a one plus reaction became negative and in another a two plus was reduced to one plus by the second test. In four cases the reaction became intensified at the second examination, in spite of vigorous treatment (one case with one plus became two plus, one with two plus became three plus, and two cases with a negative reaction became three plus).

The most important drawback to the accuracy of the test lies, to my mind, in the different preparation and efficacy of the antigen. It is well known, that the different strains of the gonococcus differ markedly one from another, in fact the difference in endotoxins is so marked, that the antibodies produced by toxins of one strain may not bind compelement in the presence of antigen prepared from another strain. It can certainly be assumed that an antigen prepared from many strains may fix complement, whenever one of its component strains does so; however, it cannot be denied, that there may exist other strains of gonoccocci, widely differing from any present in a certain polyvalent antigen of even the highest potency. Another source for discrepancy in reactions may be looked for in the difference of preparing the antigen. Viewed from this angle Hirschfelder's antigen is an uncoagulated antibody, while the two other antigens, used for our tests, are made from gonococcic strains, that have been heated to such a degree (56° C) as to render them relatively insoluble. Thus, in nine cases of my series, examined with two antigens, the positive results were uniformly one plus higher with Hirschfelder's than with McNeil's antigen.[7]

With regard to the all important marriage question, in connection with gonorrhea, the test may occasionally add confusion instead of enlightment. I observed two cases of candidates for matrimony, with a former history of gonorrhea and no clinical findings, in which the complement fixation test was three plus positive. Considering such observations, which I am sure must have been made by others, the question arises, whether

[6] N. Y. Med. Journ., Oct. 12, 1912.

[7] See also J. O. Hirschfelder, J. Am. Med. Ass'n., Dec. 11, 1915, pg. 2076.

some individuals may not be chronic gonococci-carriers. The test, on the other hand, exhibits its most important value in the so frequently met with cases of chronic prostatitis on the basis of gonorrheal antecedents, and in these cases a positive reaction is, especially in connection with the marriage question, to be considered a strict indication to postponement of the step and to vigorous local and vaccine treatment.

The best results with the test in my material were obtained in cases between six months and three years standing. It seems that beyond that time antibody formation may cease, and on this theory the explanation may be based for the negative reactions in my series of cases with long standing grave gonorrheal complications.

With regards the exacerbation of positive or the change of negative to positive results, on serological re-examination, the question arises whether a provocative reaction occurs with the test.

It is to be hoped that many of these mooted points will gradually be cleared up through constant cooperation of clinician and serologist. The test may, thus, in time assume the importance and reliability of the Wassermann reaction. For the present my own work has convinced me, that the complement fixation test for gonorrhea, if used and interpreted in connection with the clinical findings, furnishes a valuable aid to the diagnosis of latent gonorrhea.

Discussion.

Dr. A. B. Grosse: I think Dr. Krotoszyner is to be complimented on this excellent and comprehensive report which embodies a great deal of material and work. The complement fixation test as a diagnostic method is of more than ordinary interest because the general practitioner when patients come to him asking permission to marry usually base their answer on the result of the test, many times omitting the ordinary careful examinations of the genito-urinary system. For that particular reason the discussion on the efficacy of the test is particularly valuable and opportune. In my experience this procedure has been unreliable and its results should be accepted as corroborative evidence when all other examinations have been exhausted. In all probability the accuracy of this test will improve with better technic (antigen). As Dr. Krotoszyner has well said "different methods and laboratories differ much in their reports." A point not mentioned by Dr. Krotoszyner that the treatment with vaccines rendered the test useless as it is found to be positive for some time after this treatment. I might mention here a method of my own that has proved of considerable value in clearing up doubtful cases and illustrate it with the following typical history. A Salt Lake attorney whose wife was in Europe had a suspicious connection five months before. Two days following this act feeling worried, he consulted his physician who without preliminary examinations washed the urethra out with a silver solution. About two weeks later he noticed a little discharge which on examination showed no diplococci. He had no further symptoms with the exception of a feeling of fullness of the ant. urethra. A few months later he came to San Francisco and expecting the return of his wife, he thought it best to be thoroughly over-hauled. He consulted two of our well-known Genito-urinary specialists who made all the well known tests including provocative injections, etc., one of them making the complement fixation test which was frankly negative. He was assured that he was in every way safe to meet his wife. He then consulted me. The examinations made having been so exhaustive, I advised that a repetition would be useless. The only suspicious element was the appearance of the urethra and the conviction of this intelligent man that his abnormal sensations dated from the date of his coitus. I gave him daily one-third of the ordinary therapeutic dose of a potent gonorrheal vaccine with the definite intention of breaking down his resistance and creating a marked negative phase. After the fifth injection the points of injection became painful and reddened and a small amount of secretion from the urethra showed many intracellular gonococci. This method in indicated cases has proved of extreme value to me.

Dr. J. C. Spencer: Not to take up the time of the Section too only, if I may be permitted, I would like to give a brief outline of a case in my own experience bearing on the value of the complement fixation test.

A young man, single, contracted gonorrhea six years ago, complicated by epididymitis. He was treated at that time with polyvalent vaccines, to which he reacted, and subsequently apparently recovered from all symptoms of his gonorrheal infection. There was apparently no extension to his prostate and every appearance of his being free from his gonorrheal infection.

About three years later he married, feeling sure that he was perfectly safe. His marriage resulted in a healthy child. The wife was at no time infected; the child had no blenorrhea. Subsequently the man had a slight discharge about which he consulted me. I had the discharge examined culturally and found only micrococcus catarrhalis. The discharge practically disappeared.

About a year ago the patient re-appeared with a slight discharge. I told him that the complement-fixation test for gonorrhea was being used, and we tried the test, which was carried out at one of the laboratories. The report was "positive."

I will say by way of explanation, that this young man, in spite of my assurances, had always had a lurking doubt and always, previous to coitus, had injected himself with a weak solution of permanganate of potash.

About two months ago he came to me and said he was noticing a little moisture in the meatus. I found a stricture of wide calibre. This was dilated. There was a profuse purulent discharge with typical gonococci (confirmed in the laboratory). In view of the subsequent development of a typical gonorrheal relapse, he not having exposed himself and taking no chances on infecting his wife, I merely cite this as an illustration of the value of the complement-fixation test in determining what was evidently latent gonorrhea.

Dr. William E. Stevens: In this connection, a fact of importance which I have not seen mentioned in the literature has been called to my attention by Dr. Johnson of the Pacific Wassermann Laboratories:

He found that by inoculating a guinea pig with Gram positive diplococci a culture from the blood of that pig would yield Gram negative diplococci having all the cultural, morphological and staining characteristics of gonococci.

This seems to point out a fruitful field of experimentation, the results of which might have a very definite bearing upon the prognosis and treatment as well as the sero-diognosis of gonorrhea.

Dr. R. L. Rigdon: The term "strain" seems to have at least two meanings. First it relates to certain differential cultural peculiarities in the various growths obtained and second it seems to be

used to indicate growths of gonococci obtained from different patients without regard to cultural features.

I would like to enquire in which sense it is used in the discussion tonight.

Dr. M. Wolff: Dr. C. C. Worden read a paper on this subject at the last A. M. A. meeting here. He claimed that the autolysis of the bodies was due to lytic changes, due mostly to moisture. By growing the gonococci on a dry media, lysis is prevented and the fats or lipoids can be extracted. He claims that these lipoids are the active principles of the antigen, and an antigen made in this way gave him much better results in the cases he reported. We have some of his antigen and so far our results have been better, but the number of cases is not yet great enough to make a definite report. The test is important, especially when a positive is found. When a perfect antigen is found the test will be greater enhanced and this latest work seems to be a step in that direction.

Dr. E. E. Johnson: We obtain the different strains by culturing the organisms from patients suffering with different stages of the disease. For instance, we culture from several patients with a primary infection and several with a chronic infection of several months standing, and from several patients with an infection of several years standing. In the latter cases we usually culture a Gram-positive diplococcus with all the morphological characters of the gonococcus. This organism we believe to be an involutionary form of gonococcus which has lost its staining characteristics, possibly due to the acidity of the mucosa. We can also bring this organism back to its original Gram-negative staining characteristics by repeated inoculations. We always use these organisms in our gonococcus antigens.

Dr. Leonard: Can You grow gonococci from a chronic prostatic infection?

Dr. E. E. Johnson: We were unable to culture Gram-negative diplococci but succeeded in culturing, in a great many cases, the Gram-positive diplococcus which I have already mentioned.

Dr. Krotoszyner, closing discussion: I have purposely dilated in my paper upon the method in which the various antigens are prepared, in order to demonstrate, by these means, that difference in test-results, might in all probability be due to different potency of antigens. In the difficulty of obtaining an antigen of high potency lies, to my mind, the weakness of the test. This point is best illustrated by comparing the methods, by which the antigens for syphilis and gonorrhea are obtained. The antigen in syphilis is the extract of a parencymatous organ like the liver of a syphilitic foetus, while the antigen in gonorrhea is obtained from a series of cultures of gonorrhoic pus. As long, therefore, as we are not in possession of a standardized antigen, the complement fixation test for gonorrhea cannot yet assume the important position in the diagnosis of gonorrhea that the Wassermann now obtains for syphilis.

SEPTIC TEETH.

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(Continued from page 407, October issue.)

In the chronic form of the disease, if the X-ray picture shows a straight root, and only slight involvement of the bony structure about the apex, sterilization and root canal filling should be attempted, but, if it does not respond after a fair trial, it is better, in view of the dangers from chronic general sepsis to extract the tooth.

(d). Teeth which have been treated by removal of the pulp and filling of the root-canal, but in which the dentinal tubuli and fibrillae have not been thoroughly sterilized.

In an earlier portion of the paper, we called attention to the proportions of the organic and inorganic constituents of bone and dentine, and it was shown that the organic matter in dentine was nearly as great as that in bone.

We also stated the generally recognized fact that sepsis from bone and dental tissue is exceedingly virulent in character. Dr. William Hunter, of London, considers this to be the most grave of all forms of sepsis.

In the preceding remarks we have been dealing with sepsis from decomposing and gangrenous soft tissues. We now deal with sepsis as produced by the decomposition of the organic matter found in the calcified structures; namely, bone and dentine.

When nutrition is cut off from any part of the body, it dies. In other words, it is necrosed. If this happens to be a portion of the soft tissues, the necrosed portion is soon sloughed off. If it be a calcified structure, like bone, the necrosed portion is separated from the living by a somewhat similar but much slower process. Only tissues which have a blood circulation have the power to separate the dead tissues from the living.

The hard, or calcified, tissues of the teeth have no blood circulation, as a rule. The only exception is to be found—and that only occasionally—in the thicker portions of the cementum near the apex of the root, where a few haversian systems may be found.

Calcified dental tissues, therefore, have no power to separate a dead portion from a living one, and consequently have no power to reproduce tissues that has been lost by disease—as in caries, or by traumatism.

When Nature desires to rid herself of an offending tooth, a low type of chronic inflammation is set up in the pericementum and, little by little, the alveolus which gives support to the tooth is removed—in senile conditions by resorption—(senile atrophy), and in septic conditions by suppuration and caries, (molecular degeneration, or necrobiosis), and the tooth is eventually exfoliated.

Teeth of class (d) type are very rarely comfortable. They are subject to periodic attacks